CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER for: 020779, S022

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

Table 4

AG1343-515 Virology Substudy: Baseline Genotype (Protease) vs. Response[a]

	Genotypic Changes (48V, 82A/F/T/S, 84V, 90M)			
	0	1	2	3
Responders	12/14 (86%)	4/5 (80%)	2/8 (25%)	1/1
Nonresponders	2/14 (14%)	1/5 (20%)	6/8 (75%)	0/1

[a] $p = 0.016$, Fisher's exact test

APPEARS THIS WAY
ON ORIGINAL

Clinical Pharmacology & Biopharmaceutics Review

NDA 20-779 (SE8-022)	**Submission Dates:** 01/07/99, 01/26/99
Nelfinavir mesylate (VIRACEPT™)	**Logged In:** 02/04/99
Agouron Pharmaceuticals, Inc.	**Draft Review:** 06/08/99
Type of Submission: Supplemental NDA	**Final Review:** 06/10/99
	Reviewer: Brad Gillespie, PharmD

Background Nelfinavir mesylate 250 mg tablets received accelerated approval on March 14, 1997 for the treatment of HIV infection at a recommended dose of 750 mg three times daily. In this supplement, the sponsor has included information to support the implementation of a 1250 mg twice daily dosing regimen. In addition to clinical safety and efficacy data, the sponsor has included a pharmacokinetic subset analysis designed to compare the pharmacokinetics of nelfinavir and its major active metabolite (AG1402), when administered as both regimens. In this review, this comparative trial and three drug-drug interaction trials (Efavirenz, nevirapine, rifabutin) are evaluated. A comprehensive review and discussion of each individual study begins on Page 4.

Synopsis The most critical feature of this application, from a pharmacokinetic standpoint, is the comparison of nelfinavir BID versus TID. In a Phase 3 trial (Study AG1343-542), subjects were randomized to receive lamivudine and stavudine with either: 750 mg TID, 750 mg BID, 1000 mg BID or 1250 mg BID nelfinavir. Although this trial was not adequately designed to give a definitive pharmacokinetic comparison, it suggests that oral nelfinavir bioavailability, as measured by C_{max} and AUC, after BID dosing (750, 1000 and 1250 mg) is greater than that observed after 750 mg TID dosing (AUC +1 to 21%; C_{max} +22 to 43%). The exposure to AG1402 was variable across arms. Nelfinavir plasma concentrations at the end of the dosing interval, though, are projected to be lower (-28 - 54%), introducing the possibility of resistance emergence. In fact, based on the assumption of linearity, in order to obtain comparable trough concentrations, a BID dose of 1800 mg would be required. Therefore, in order to approve this application, it is critical that the safety of higher peak and reduced trough concentrations following BID dosing are clearly characterized, both clinically and microbiologically.

In addition to the comparative pharmacokinetic study, this review also evaluates three nelfinavir drug-drug interaction studies. In the first, the sponsor dosed full (300 mg, daily) and half-dose (150 mg, daily) rifabutin concomitantly with 750 mg TID and 1250 mg BID nelfinavir regimens. This study demonstrated that, although the decreases in nelfinavir plasma concentrations when given with rifabutin are not of a large magnitude (approximately 0 – 20%), the possibility of reduced efficacy cannot be excluded. Especially worrisome is the mean 32% drop in nelfinavir end of dosing interval concentration. Depending on the minimum effective concentration for nelfinavir, such decreases could be associated with the emergence of viral resistance. The major increases in rifabutin and desacetylrifabutin (major metabolite) concentrations when dosed with nelfinavir (150 mg with nelfinavir vs 300 mg alone: rifabutin AUC +83%, C_{max} +19%; desacetylrifabutin AUC +1248%, C_{max} +547%) may lead to the occurrence of increased adverse events. The clinical relevance of this interaction is unknown.

In the second drug-drug interaction study, nevirapine was dosed concomitantly with nelfinavir. This trial was not designed to describe the effect of nelfinavir on nevirapine and did not include data to describe the effect of nevirapine on nelfinavir's major metabolite, AG1402. Therefore, even though nevirapine does not appear to appreciably effect the pharmacokinetics of nelfinavir, as submitted, this study report does not support any labeling claims.

In the third drug-drug interaction trial, the sponsor concomitantly dosed efavirenz and nelfinavir. Nelfinavir at a dose of 750 mg q8hr did not alter the steady state AUC_τ or C_{max} of efavirenz at a dose of 600 mg qhs. Efavirenz at a dose of 600 mg qhs increased nelfinavir AUC_τ by approximately 20% and C_{max} by approximately 21%. The results were similar when efavirenz 400 mg qd was administered with nelfinavir 750 mg q8hr. The changes observed in this study were not clinically significant. Efavirenz and nelfinavir may be coadministered together without adjusting the dose of either drug. These findings should be addressed in revised package labeling for both products.

At this time, neither clinical, not microbiological interpretations of the results reported in the BID vs TID pharmacokinetic trial or the rifabutin interaction trial are available for inclusion in this review, but should be followed up on, as needed. A followup review will be written to address these issues at a future time.

Comments

Comment 1 refers to Study AG1343-542

1. The sponsor is requested to provide individual patient $AUC_{0-\tau}$ values and a description of how these values were scaled to determine AUC_{0-24}. Until this information is provided and validated by FDA, AUC values included in the submission should be viewed as preliminary.

Comments 2 – 4 refer to Study BI 1100.1224

2. This study was not designed to characterize the pharmacokinetic effect of nelfinavir on nevirapine. If the sponsor wishes to include language based on historical data, they will need to submit a more rigorous comparison to any existing information.
3. The sponsor is requested to submit representative chromatograms from the nevirapine assay to establish its specificity.
4. The sponsor is requested to provide individual and mean concentration versus time data for nevirapine and AG1402. Additionally, they are requested to submit individual and mean pharmacokinetic parameter estimates for AG1402 both with and without nevirapine.

Recommendation This supplemental application and drug-drug interaction study reports have been reviewed by the Office of Clinical Pharmacology & Biopharmaceutics which has determined that there are significant differences in the pharmacokinetic profiles of BID and TID-dosed nelfinavir. These findings have been communicated to the clinical

review team, which will determine if these differences are relevant. In addition, the Office has determined that nelfinavir's labeling should be modified to reflect the results of the drug-drug interaction trials with efavirenz and rifabutin once their clinical relevance is determined. Some labeling language may be derived from the nevirapine trial, depending on the quality of their response to the Comments, above.

Please forward Comments 1 – 4 to the sponsor.

A phase III study comparing BID and TID dosing of viracept in combination with stavudine (d4T) + lamivudine (3TC) in HIV-positive patients
Study No. AG1343-542 **Volume** 41.18
Investigator Multi-Center
Clinical Dates 3/11/97 – 7/31/98
Analytical Facility [redacted]
Analytical Dates 7/25/97 – 8/13/97

Objectives To compare the multi-dose pharmacokinetics of nelfinavir after twice- (750 mg, 1000 mg, 1250 mg) and three-times daily dosing (750 mg) and when given in combination with d4T and 3TC

Study Design A total of 459 adult male and female HIV patients at 21 sites were included in this randomized, double-blind, multiple-dose, 2-treatment, parallel trial. A total of 299 patients were randomized to the BID treatments while 160 were dosed TID. Trough plasma samples were collected at selected sites during each clinic visit from baseline to Week 48, while the pharmacokinetics of nelfinavir were extensively studied in a subset of patients from each dose regimen (750 mg BID: n=9; 1000 mg BID: n=9; 1250 mg BID: n=10; 750 mg TID: n=11) after the morning dose at Week 4.

Sampling
Blood samples were obtained for plasma nelfinavir (AG1343) and its major metabolite, AG1402, determinations just prior to (zero hour), 1, 2, 3, 4, 5, 6 and 8 hours after study drug administration. For patients receiving the BID regimens, the sponsor also collected 10 and 12 hour samples.

Assay An [redacted] method was used for plasma AG1343 and AG1402 determinations

[redacted]

Data Analysis
Pharmacokinetic: - C_{max}, C_τ[1] T_{max}, $AUC_{0-\tau}$

[1] Plasma concentration at the end of the dosing interval

Statistical: In order to facilitate comparison of the TID and BID regimens, AUC values were scaled to a 24 hour period. This process was not described in the submission. Descriptive statistics were included in the submission for all pharmacokinetic parameters.

Results All of the selected patients completed the pharmacokinetic subset phase of the study. The mean plasma AG1343 and AG1402 concentration versus time profiles for the first 8 and 12 hours (for the TID and BID regimens, respectively) after dosing are presented in Figures 1 and 2. Pharmacokinetic parameters are presented in Table 1. Trough plasma concentrations from the non-pharmacokinetic subset were not listed in the study report.

Figure 1. Mean Plasma Nelfinavir Concentrations After Multiple Oral Doses of 750 mg BID, 1000 mg BID, 1250 mg BID and 750 mg TID for Four Weeks

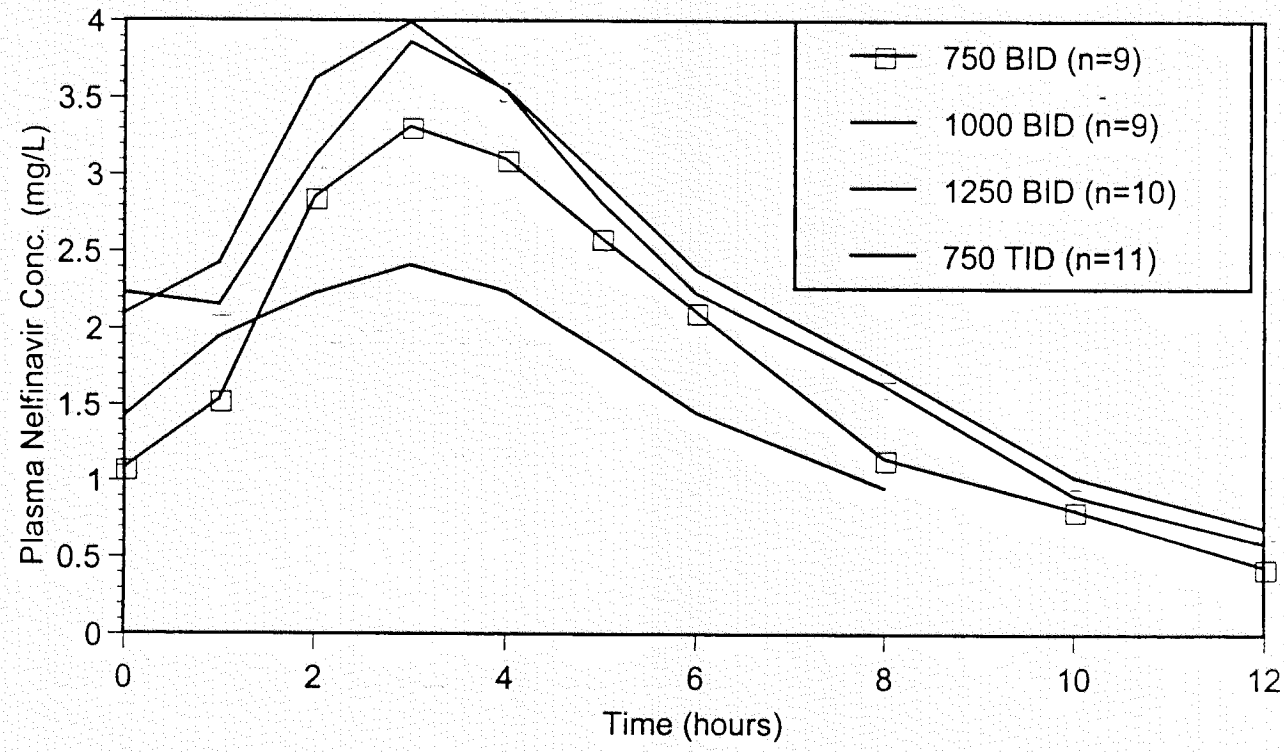


Figure 2. Mean Plasma AG1402 Concentrations After Multiple Oral Doses of 750 mg BID, 1000 mg BID, 1250 mg BID and 750 mg TID for Four Weeks

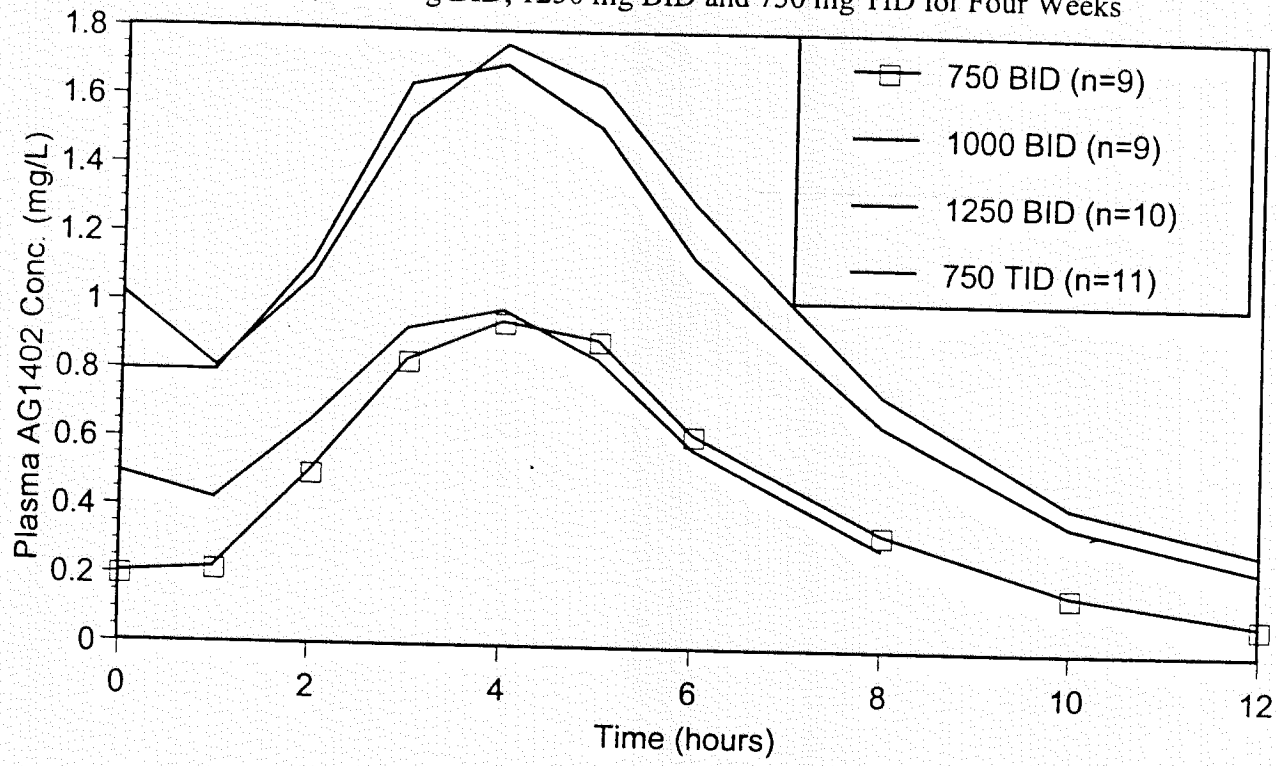


Table 1. Arithmetic Mean (%CV) Nelfinavir (AG1343) and AG1402 Pharmacokinetic Parameters After Multiple Oral Doses of 750 mg BID, 1000 mg BID, 1250 mg BID and 750 mg TID for Four Weeks

Parameter	*Unit*	*750 BID (n=9)*	*1000 BID (n=9)*	*1250 BID (n=10)*	*750 TID (n=11)*
AG1343 AUC_{24}	mg·h/L	44.0 (47)	52.8 (24)	52.8 (30)	43.6 (41)
AG1343 C_{max}	mg/L	3.59 (33)	4.24 (18)	3.99 (20)	2.96 (54)
AG1343 C_{τ}	mg/L	0.439 (56)	0.551 (49)	0.694 (61)	0.958 (48)
AG1343 T_{max}[2]	h	3 (2-4)	3 (2-4)	3.5 (2-5)	3 (0-5)
AG1402 AUC_{24}	mg·h/L	11.1 (62)	22.3 (56)	23.8 (46)	15.7 (60)
AG1402 C_{max}	mg/L	1.03 (55)	1.78 (47)	1.85 (32)	1.10 (59)
AG1402 C_{τ}	mg/L	0.0973 (73)	0.227 (69.5)	0.296 (78.9)	0.300 (67)
AG1402 T_{max}[2]	h	4 (3-5)	4 (3-4)	4 (3-5)	4 (0-5)

Comment The sponsor is requested to provide individual patient $AUC_{0-\tau}$ values and a description of how these values were scaled to determine AUC_{0-24}. Until this information is provided and validated by FDA, AUC values included in the submission should be viewed as preliminary.

Discussion It is important to preface any conclusions drawn from the data presented here by acknowledging that they were obtained in a Phase 3 clinical trial. While these

[2] *Median (range)*

data are important in a descriptive sense, it is critical to note that these types of trials are inherently more variable than well controlled Phase 1 studies. Additional variability can be expected due to, but not limited to, any of the following factors: concurrent disposition-influencing disease states in patients (versus healthy volunteers); decreased power of parallel versus crossover trial design; concomitant medications, or decreased sensitivity of multiple-dose trials. Also, although both parent nelfinavir and its major active metabolite AG1402 are similarly potent *in vitro,* nelfinavir is probably the most critical moiety for analysis owing to its higher achieved concentrations (C_{max} and AUC parent:metabolite ratios of 2.16 and 2.22, respectively at a dosage of 1250 mg BID). With these caveats in place, it is evident that nelfinavir AUC (as calculated by the sponsor) and C_{max} after BID dosing at any of three dose levels exceeds that observed after administering 750 mg TID. So, while efficacy should not be a concern, these levels should be interpreted in light of the available safety database for this product. Also of interest is C_τ. Since adequate plasma concentrations at the end of the dosing interval are critical to limiting the emergence of resistant organisms, this is a critical parameter for evaluation. C_τ is substantially lower after administration of all of the BID regimens compared to TID dosing. The distributions of C_τ after TID and BID dosing are presented in Figure 3. By inspection, it is evident that while there is overlap between the two regimens, lower troughs can be expected after BID dosing. Since observed C_τ levels are very nearly linear with regard to dose ($r^2 = 0.9951$), it is possible to estimate, through extrapolation, that a dose of approximately 1800 mg BID would be required to achieve a C_τ comparable to that achieved after administration of 750 mg TID (Figure 4). Naturally, the need to decrease the risk of emerging resistances using an increased dose (compared to proposed dose of 1250 mg BID) should be balanced against the risk of increased toxicity associated with largely increased peak plasma concentrations. Lastly, since in this Phase 3 trial, all subjects were concomitantly receiving 3TC and d4T (interaction potential with nelfinavir unlikely), and many were also taking other medications, the possibility of drug-drug interactions cannot be excluded.

Conclusion Although this trial was not adequately designed to give a definitive pharmacokinetic comparison, it suggests that oral nelfinavir bioavailability, as measured by C_{max} and AUC, after BID dosing (750, 1000 and 1250 mg) will be greater than that observed after 750 mg TID dosing. Nelfinavir plasma concentrations at the end of the dosing interval, though, are projected to be lower, introducing the possibility of resistance emergence. Therefore, in order to approve this application, it is critical that the safety of higher peak and reduced trough concentrations following BID dosing are clearly characterized, both clinically and microbiologically.

Figure 3. Distribution of Individual Patient C_τ After Multiple Oral Doses of Nelfinavir 750 mg TID and 1250 mg BID

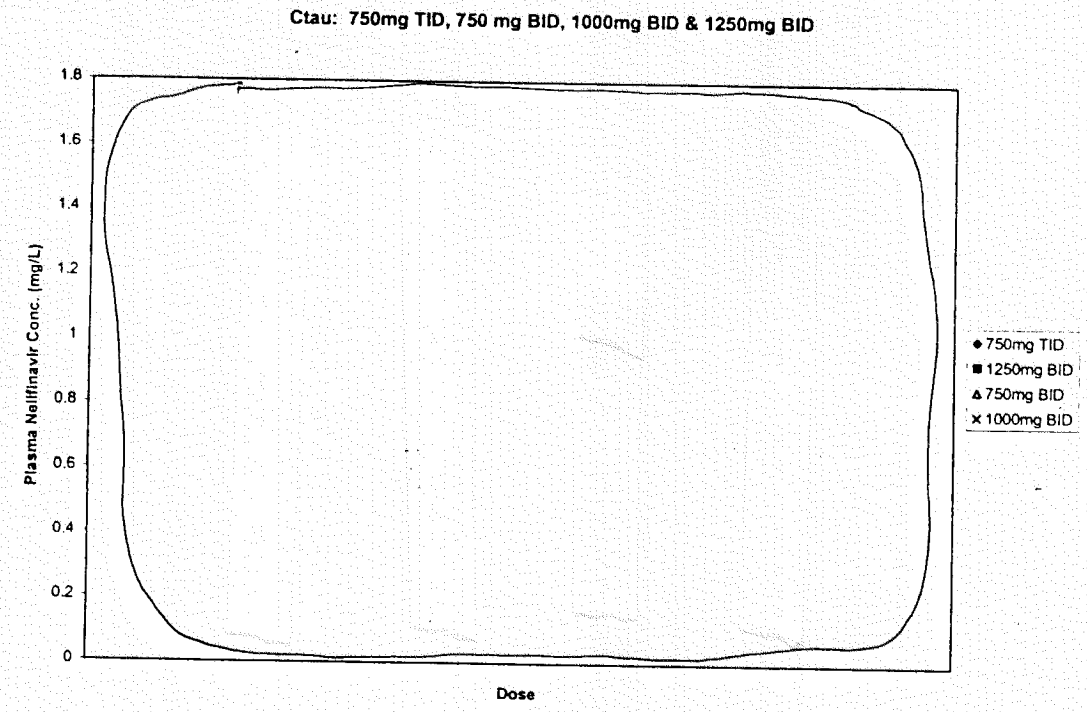
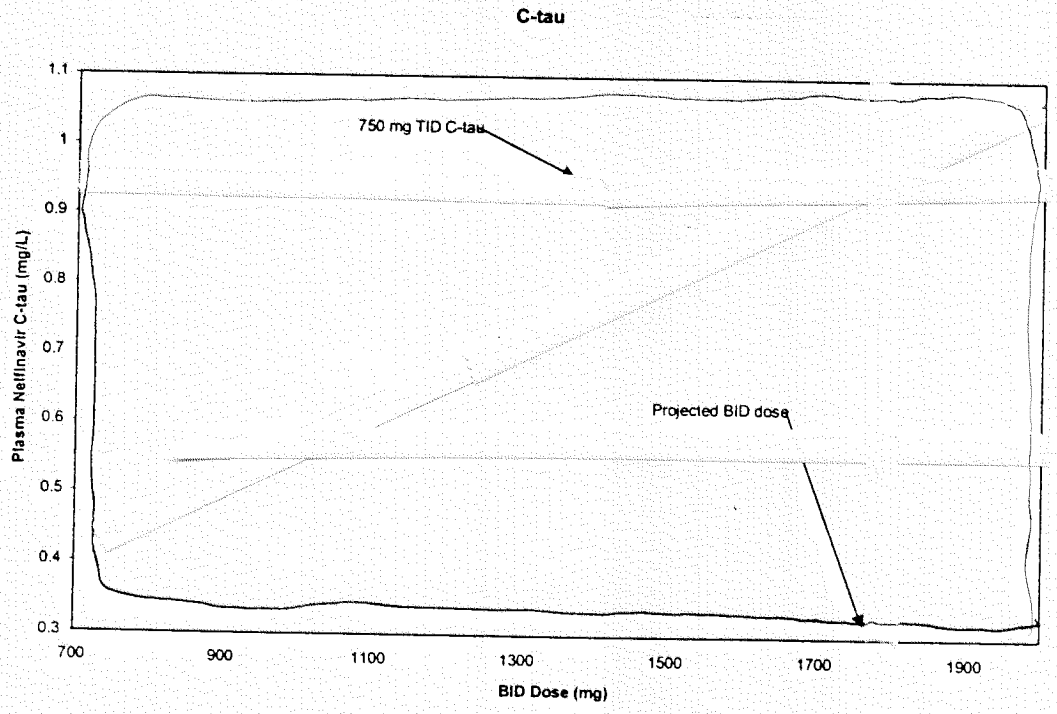


Figure 4. Observed and Projected C_τ Values After Oral Administration of Nelfinavir BID



A pharmacokinetic study of the interaction between viracept and reduced dose rifabutin

Study No. AG1343-649 **Volume** 41.3 – 41.7

Clinical Dates 10/26/97 – 12/14/97

Analytical Facility Nelfinavir and metabolite
Rifabutin and metabolties

Analytical Dates Nelfinavir and metabolite: 12/18/97-12/30/97. Rifabutin and metabolites: 5/4/98-5/21/98

Objectives (a) To determine the effect of multiple-dose rifabutin (150 mg: half the normal dose, for 8 days) on the pharmacokinetics of nelfinavir after multple dosing (750 mg every 8 hours for 7.33 days). (b) To compare the pharmacokinetics of multiple doses of rifabutin (300 mg: full dose, for 7 days) in the absence of nelfinavir to multiple-dose rifabutin (150 mg for 7 days) pharmacokinetics when given concomitantly with nelfinavir (750 mg every 8 hours for 7 days). (c) To determine the effect of multiple doses of rifabutin (150 mg for 8 days) on the pharmacokinetics of nelfinavir after multiple doses (1250 mg every 12 hours for 7.5 days).

Formulations

Nelfinavir (Viracept®) 250 mg tablets, Lot No. 087467
Rifabutin (Mycobutin®) 150 mg tablets, Lot No. RIF 050

Study Design A total of 41 healthy, non-smoking adult male and female subjects were included in this open-label, 3 parallel group, randomized, multiple-dose, 2-treatment, 2-period crossover study. Subjects were initially randomized to three groups (A, B or C) and were then further randomized within group to sequences receiving A1 and A2, or B1 and B2 or C1 and C2. Subjects received both intra-group treatments in a crossover fashion with a 13 day washout period separating the treatments. The treatments administered are described below:

A1: 750 mg nelfinavir Q8hr for 7.33 days
A2 750 mg nelfinavir Q8hr for 7.33 days + 150 mg rifabutin QD for 8 days

B1 300 mg rifabutin QD for 7 days
B2 750 mg nelfinavir Q8hr for 7.33 days + 150 mg rifabutin QD for 8 days

C1 1250 mg nelfinavir Q 12hr for 7.5 days
C2 1250 mg nelfinavir Q 12hr for 7.5 days + 150 mg rifabutin QD for 8 days

Subjects checked into the study facility the evening before dosing and remained confined until after the last blood sample was collected. Each dose was administered with a light meal or snack. On the pharmaceutical evaluation days, study medications were given

after a standardized light breakfast. Subjects abstained from alcohol and caffeine-containing foods and beverages during the study period.

Sampling

Blood samples were obtained for plasma nelfinavir (and metabolite) and rifabutin (and metabolite) determinations just prior to (zero hour), 0.5, 1, 2, 3, 4, 5, 6 and 8 hours after study drug administration. Additional samples were collected from subjects receiving Treatment C1 and C2 10 and 12 hours after dosing for nelfinavir concentrations while subjects receiving rifabutin (Treatments A2, B1, B2 and C2) also had samples drawn 12, 18 and 23 hours after dosing.

Assay methods were used for plasma determinations of nelfinvair, AG-1402 (its active metabolite), rifabutin and its active desacetyl metabolite

Data Analysis
Pharmacokinetic: C_{max}, T_{max}, C_τ[3], $AUC_{0-\tau}$, Cl/F
Statistical: The sponsor calculated descriptive statistics for all parameters

Results Thirty-five of the original 41 subjects completed the trial. Those that withdrew did so for a variety of reasons not related to the use of study drug. One of the plasma samples of these 35 subjects was misplaced so a total of 34 subjects were included in the final analysis (Group A: 11; Group B: 12; Group C: 11). Mean plasma concentration versus time profiles for the various comparisons are presented in Figures 5 - 10. Pharmacokinetic parameters are presented and compared in Tables 2 – 7.

Discussion When nelfinavir is given as a 750 mg TID dose concomitantly with half-dose (150 mg daily) rifabutin, its bioavailability (as measured by C_{max}, AUC and C_τ) is decreased by a factor of approximately 20%, with a similar effect on its major metabolite, AG1402. When given as a 1250 mg twice daily regimen, the parent nelfinavir peak plasma concentration was not changed appreciably while the concentration at the end of the dosing interval and total exposure (AUC) were decreased by 32% and 6%, respectively. With regard to the metabolite (AG1402), AUC was increased (+24%) while there was no change in C_{max} or C_τ. Nelfinavir reduces the clearance of rifabutin to the point where the bioavailability of a 150 mg daily dose with nelfinavir is substantially higher than after a 300 mg dose alone (C_{max} +19%, AUC +83%). The effect on the metabolite, desacetylrifabutin, is even greater: C_{max}: +547%, AUC +1248%.

Conclusion Although the decreases in nelfinavir plasma concentrations when given with rifabutin are not of a large magnitude, the possibility of reduced efficacy cannot be excluded. Especially worrisome is the 32% drop in nelfinavir concentration at the end of the dosing interval. Depending on the minimum effective concentration for nelfinavir, such decreases could be associated with the emergence of viral resistance. The clinical significance of this interaction is unknown. The major increases in rifabutin/desacetylrifabutin concentrations may lead to the occurrence of increased adverse events. The literature describes a number of adverse events to include a reduction in white blood cell count, gastrointestinal symptoms, abnormal liver enzymes, diffuse polyarthalgia syndrome and anterior uveitis. Particular concern has centered around the dose-related adverse event uveitis. These findings should be addressed in revised package labeling for both products.

[3] Plasma concentration at the end of the dosing interval